REMARKS

Reconsideration of this application is requested. Claims 1-13 remain active in the application subsequent to entry of this amendment.

It is proposed to amend claims 1-3 in order to more clearly define applicants' invention and to address the issues raised in item 2 of the Official Action.

Claim 1 is amended to be internally consistent, responsive to the last paragraph of page 2 of the Official Action while claim 2 has been revised and rewritten in independent format. It clarifies that there may be at least one phospholipid present and also, optionally a surfactant other than phospholipid. Applicants recognize and in some instances, phospholipids are in fact surfactants. The proposed wording clarifies the claims and responds to the examiner's request.

Claim 3 includes a number of additional ingredients which may be present in the compositions which ingredients, in turn, are the subject of various dependent claims (4-8). While counsel disagrees with the examiner's analysis of the "consisting essentially of" terminology used in claim 1, in order to advance prosecution, it is proposed to revise claim 3 and state it in independent format. As a consequence, dependent claims 4-8 define specifically mentioned constituents of newly independent claim 3. Claims 9 and 11-13 relate to properties of the compositions, not components directly, and thus are not of concern. Claim 10 merely provides for the presence of an effervescent couple present in the composition.

The art-based rejections, items 3-7 of the Official Action, are all based essentially on the disclosures of Green, U.S. Patent No. 5,976,577. Claim 1 of Green '577 claims:

Clear distinctions from the present invention will be apparent through Greer patent.

> "A process for preparing an oral solid rapidly disintegrating dosage form of a pharmaceutically active substance, comprising the steps of: forming a suspension in a continuous phase of **coarse particles** [1]of a pharmaceutically active substance in a carrier material, said carrier material being selected from the group consisting

[1] indicates emphasis added

> of water-soluble and water-dispersible carrier materials; reducing the temperature of the suspension to form a cooled suspension of increased viscosity; forming discrete units of said cooled suspension; and removing the continuous phase to leave said rapidly disintegrating form in said carrier material."

and

> Column 2, lines 29-35 of Green '577 teaches:
>
> "... provides such improved rapidly disintegrating dosage forms and processes for their preparation **by allowing processing of coarse coated particles** without affecting the physical properties of the dried units. The invention can also be **used to enable processing of coarse uncoated drug material**, preventing the need to obtain size reduced material and an additional manufacturing stage."

and

> Column 2, lines 61-62 of Green '577 teaches:
>
> "... comprising forming **a suspension (i)n a continuous phase of coarse particles** of the pharmaceutically active substance ..."

The invention of Green '577 is directed to coarse particles that can be coated or uncoated (coarse particles are specified 13 times in the Green '577 patent). However, the present invention of Parikh (Parikh '863) is directed away from coarse particles (i.e., those of Green which are up to 1 millimeter in size), and teaches the requirement for "primary particles" or (see page 1, line 7) "small surface coated particles" (that are less than 10 microns). Small particles that are not surface modified are known to be unstable toward particle size growth and agglomeration particularly in an aqueous environment. Thus, in the Parikh '863 invention, non-surface modified particles are not suitable as Parikh requires that the particles be dispersable in an aqueous medium.

(a) Claim 4 of Green '577 claims:

> "A process according to claim 1, wherein said **coarse particles are uncoated or coated** with a coating which **delays release of the pharmaceutically active substance** beyond the point of disintegration of said form on the tongue."

and

> Column 1 lines 8-12 of Green '577 teaches:

> "The drug particles **may be uncoated or coated** with a water-insoluble polymer or lipid material which **prevents release of the drug during processing**, masks the taste of the drug in the mouth, and **permits controlled release of the drug after swallowing**."

Green '577 teaches that his large, coarse, uncoated or coated drug particles are formulated to prevent release of drug during processing and to permit controlled release of the drug after swallowing. Green does not teach enhancement of bioavailability in his coarse particles. The present invention of Parikh (Parikh '863) requires the "primary particles" to be of nominal diameter of 0.05 to 10 micrometers (see page 1, line 3), stabilized by at least one surface modifying agent of which one is a phospholipid adsorbed on the surface of the particle (page 4, lines 9-10), and the bulking/releasing agents be chosen in order to produce a matrix that, upon drying, will yield dispersible tablets that release the primary particles upon reconstitution in an aqueous medium.

The inventive phospholipid stabilized particles promote and facilitate the release of the pharmaceutically active substance [i.e., provide enhanced bioavailability]. Parikh '863 teaches that "small particle sizes of" water-insoluble "drugs are often needed in drug formulation development in order to maximize surface area, bioavailability, and dissolution requirements." (page 4, line 20-21). Further, "The matrix-forming agent used in the present invention must dissolve or disperse upon contact with an aqueous environment and release the phospholipid coated therapeutic agent particle. Upon reconstitution, the product reverts to a suspension having the same degree of dispersity at the pre-dried suspension." (see pages 8, lines 31-33 and page 9, line 1). This redispersion to a suspension of very small particles stabilized by a phospholipid is not taught by Green '577 who teaches coarse uncoated or coated particles. The present invention of Parikh (Parikh '863) also teaches "The rate of dissolution or release of the active ingredient may also be affected by the nature of the medicament and the microparticle composition such that it may be rapid (5-60 sec) or intermediate (on the order of 75% disintegration in 15 minutes) or sustained-released. (see page 9, lines 22-24). This is not taught by Green '577 which teaches only delayed release of the pharmaceutically active substance.

Claim 10 of Green '577 claims:

> "A process according to claim 1, wherein said coarse particles have a size in the range of 50 μm to 400 μm..."

The present invention of Parikh (Parikh '863) requires that the particles are substantially smaller in size, i.e., in the range of 0.05 to 10 micrometers (see page 1, line 3). Further, on page 12, lines 5-6, the present invention of Parikh (Parikh '863) teaches "... in order to appreciably affect bioavailability, particles which are an order of magnitude less in size are required. [i.e., primary particles that are about 1 micrometer]. The invention of Green '577 teaches large particles while the invention of Parikh (Parikh '863) teaches away from large particles, opposite to the teaching of Green '577 and not anticipated by Green '577.

(b) Column 2, lines 48-53 of Green '577 teaches:

> "This (minimal release of the drug in the mouth) is **achieved by using coarse coated drug particles** and controlling the viscosity of the suspension by reducing the temperature during the holding time in suspension to **minimize sedimentation of the particles** without altering the physical properties of the dried units."

The present invention of Parikh (Parikh '863) teaches that the particles need to be small rather than coarse, will be redispersed to a suspension of small particles rather than undergo sedimentation, does not teach controlled release but rather increased bioavailability, and does not teach control of sedimentation by viscosity enhancement.

(c) Column 3, lines 6-22 of Green '577 teaches:

> "Size of the particles has an important effect on the rate of release of drug when coated. A smaller particle has a much larger overall surface area for diffusion. As a result, **the rate of release of drug is greater the smaller the particle.** Current **coating techniques are able to effectively coat particles greater than 100 micrometers, whereas particles less than 100 micrometers may not have an intact coat, which will result in rapid release of the drug once in suspension.** Coating of larger particles therefore decreases the rate of release of drug. Typically, **according to the present invention, the coarse particles may have a size of up to 1 millimeter, although the average size is generally up to about 500 micrometers for example 75 to 400 micrometers, more usually in the region of about 100-300 micrometers.** In this size range, it is possible to apply a uniform intact coating on the particle in order to achieve efficient freeze-dried dosage forms with slow drug release rate."

Green in '577 acknowledges that small particles have a greater release rate of drug than do larger particles. Green '577 teaches that particles with size larger than 100 micrometers can be coated effectively but teaches that particles less than 100 micrometers cannot be coated effectively according to his invention. Particles below 100 micrometers will undergo rapid release of the drug. Green directs his invention to large particles up to 1 millimeter in size with an average size generally up to about 500 micrometers. Unlike Green '577, the present invention of Parikh (Parikh '863) teaches the use of very much smaller particles which have enhanced drug release properties and which do not form sediments. Examples 3 and 4 in Table 1 of the present invention of Parikh (Parikh '863) show significant increases in particle size between pre- and post-lyophilization (i.e., particles grow in examples 3 and 4 from 0.66 and 0.91 micrometers pre-lyophilization to 48.9 and 85.5 micrometers post-lyophilization, respectively), and are acknowledged in Parikh '863 to be outside the scope of that '863 invention:

"Examples 3-5 illustrate that certain microparticle compositions do not reconstitute favorably when traditional cryoprotectants such as lactose or PVP17 are used as described in US Patent 5,302,401. For these examples, large aggregates are formed comprised of adhering primary particles."

For a lyophilized product to fall within the scope of the present invention of Parikh (Parikh '863) it is required upon reconstitution that "the product reverts to a suspension having the same degree of dispersity as the pre-dried suspension." (see pages 8, lines 31-33 to page 9, line 1). The post-lyophilization aggregates in examples 3 and 4 are unacceptably large in size, yet are still small in size with respect to the large coarse particles taught by Green '577. Clearly the inventions address two different concepts.

(d) Column 3 lines 23-33 of Green '577 teaches:

"Increasing the particle size **gives rise to increased sedimentation rate** of the particles in suspension. **This causes difficulties in obtaining uniformity of dose** in each dosage form and **can also cause splitting of the units if the drug particle sediments in the individual blister pockets before being frozen**. The present **invention overcomes this problem** by adjusting the viscosity by reducing the temperature of the fluid suspension by an amount such as to increase the viscosity to a

level sufficient to prevent or substantially eliminate settling out of the drug particles, ..."

Green in '577 acknowledges that his invention employs larger size particles and that they are prone to form sediments. Green establishes that his invention addresses the prior art needs related to large particles, i.e., difficulties in obtaining uniformity of dose, and sedimentation from suspension in the individual blister pockets. His solution is to increase the viscosity of the carrier by lowering temperature before sedimentation occurs. The present invention of Parikh (Parikh '863), however, teaches away from Green '577, i.e., it does not teach that the particles are coarse or large but rather that they are small, and that the particles are not prone to form sediments but rather must redisperse to a suspension of the original particles.

(e) Column 3 lines 61-64 of Green '577 teaches:

"It is possible to **adjust the viscosity of the suspension sufficiently to prevent rapid sedimentation of drug particles up to 400 micrometers.** The use of **particles in this size range can prevent release of drug** during the mixing stage."

and

Column 6, lines 1-4 and lines 6-8 of Green '577 teaches:

"According to the process of the invention, **sedimentation in the drug suspension in the carrier material is controlled by manipulation of the matrix temperature** to create a more viscous solution. ..."

Green in '577 controls sedimentation by manipulation of the matrix temperature. Green '577 acknowledges that the drug particles can undergo rapid sedimentation related to their large size, but also teaches that the size of these large particles prevents release of drug. In each of Green's examples, % sedimentation versus time is measured as a gauge of the efficacy of reduction of temperature and increase in viscosity. The present invention of Parikh teaches (see page 2, lines 22-24) that suspensions of water insoluble compounds are likely to sediment prior to completion of the freeze-drying or spray drying process leading to [undesirable] particle aggregation and potentially inhomogeneous dry dosage forms."

(f) Column 4 lines 23-26 of Green '577 teaches:

> "A further advantage realized in the use of temperature modification of the suspension is the consequent **decrease in the rate of release of drug from particles which have been coated**."

Green in '577 teaches that his invention provides as an advantage a **decrease in the rate of release of drug** leading to enhanced bioavailability from large, coarse particles which have been coated, whereas the present invention of Parikh (Parikh '863) teaches an increase in release of drug from small particles that are redispersed in an aqueous medium to reform their original suspension.

Surface coatings and surface modifiers are also important considerations. The present application describes a rapidly dispersing system consisting of "nanometer or micrometer particulate solid" (of a water insoluble drug) "which is surface stabilized with one or more surface modifiers of which at least one is a phospholipid...." These particles, including the surface coating, are typically in the range of 50 nm to 10 microns. The surface modifiers, also termed amphipathic surfactants, coat the surface and are specifically selected such that the hydrophobic (or amphiphobic) end of the surface modifier orients towards the surface of the water-insoluble drug. The hydrophilic (or amphiphilic) orients away from the surface. These surface modifiers allow the formation of these very small particles and stabilization especially in aqueous environments. The structure of these particles and specific role of the surface modifier or amphipathic surfactant is described in more detail in Pace *et al* – Pharmaceutical Technology, March, 1999, p120, 122 (copy attached) and Haynes, U.S. Patent No. 5,091,187 & 5,091,188.

On the other hand, Green (US 5,976,577) (Column 3, lines 15 –18) describes "coarse particles ... up to a size of 1 millimeter, although the size is generally up to about 500 μm, for example 75 to 400 μm, more usually in the region of about 100-300 μm. In this size range, it is possible to apply a uniform intact coating on the particle to achieve freeze dried dosage forms with slow drug release rate." The coating of particle to control release rate of the drug is well established technology (Remington Pharmaceutical

Sciences, p 1645, copy attached). The role of the coating material is to form a barrier to water and slow the dissolution of the drug.

Green (Column 5, lines 31 – 34) says that

"the coating on the particles is a polymer or lipid material and serves to prevent loss of the pharmaceutical agent during processing, as well as delaying the release of the pharmaceutically active substance beyond the point of disintegration of the form in the mouth."

Thus the role of the coating material in Green is fundamentally different from the amphipathic surfactant or surface modifiers coating materials comprised in the particles described and claimed in the present application. Green does not teach the importance of the nature of the surface modifier and its role in the formation and stabilization of the particles described in the present application.

Further, Green does not claim or teach in the examples that the surface coating materials orient at the drug surface to allow formation and stabilization of the small particles or indeed there is any change in particle size using his methods. In addition, Green teaches his process and compositions apply to both water-soluble and insoluble drugs. By contrast, applicants' claims are restricted to only a composition that includes "nanometer to micrometer" particles of water-insoluble drugs and requires a specific interaction between the selected surface modifier (coating material) and the surface of the water-insoluble drug particle.

Applicants have noted the content of the Libby patent, U.S. Patent No. 4,432,975, and agree that it suggests the use of polyethylene glycol in quick dissolving formulations. However, claim 5 is believed to be fully patentable based upon the patentability of the claim from which it depends, claim 3. Similarly, applicants acknowledge that the Carli patent, U.S. Patent No. 5,164,380, relates to including colloidal silica to facilitate disintegration and various formulations. Again, applicants submit that claim 7 is patentable by virtue of its dependency from a broader claim that is patentable, claim 3.

Reconsideration of this application, entry of this Amendment and favorable action are solicited.

Respectfully submitted,

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